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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/576,858	05/22/2000	Richard O. Snyder	40447	2597

7590 11/28/2001

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	PAPER NUMBER
1632	11

DATE MAILED: 11/28/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Acti n Summary	Application N .	Applicant(s)	
	09/576,858	SNYDER ET AL.	
	Examiner	Art Unit	
	Scott Priebe	1632	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7,15,16,20,26,27,31,32,36,39,43,48 and 54* is/are pending in the application.

4a) Of the above claim(s) *48 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7,15,16,20,26,27,31,32,36,39 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction

Applicant's election of Group I, claims 1, 4, 7, 15, 16, 20, 26, 27, 31, 32, 36, 39, and 43 in Paper No. 10, filed 9/19/01, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 48 and 54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). The claim to benefit to the provisional application must appear as the first sentence/paragraph of the specification (after the title) in order to comply.

The first sentence of the application must indicate the priority claim to 08/882,044 and 60/032,552 applications.

Specification

The disclosure is objected to because of the following informalities: The vector shown in Fig. 6 is referred to by several different names, "rAAV-MFG-human-Factor IX" (page 12, line 6), "AAV-MFG-hFIX" (page 38, line 33), and "AAV-MFG-Human Factor IX" (page 39). One single name should be chosen for the vector and used throughout the specification. Appropriate correction is required.

Claim Objections

Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 1 recites that viral particles comprising an AAV vector are administered to liver cells "such that said polynucleotide, or portion thereof, is expressed in said mammal". Claim 4 recites liver cells are "transduced with said AAV vector ex vivo" and the cells are delivered to the mammal. The only way that "administering viral particles" (claim 1) to liver cells can result in expression in a mammal of a polynucleotide contained in the particles, is if the liver cells were already in the mammal, i.e. *in vivo* transduction. The subject matter of claim 4 is not embraced by the method of claim 1, since "administering" the viral particles to the liver cells *ex vivo* does not result in expression in a mammal, but in a culture flask, for example.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 7, 15, 16, 20, 26, 27, 31, 32, 36, 39, and 43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of expressing a polynucleotide in a mammal (claims 1, 4, 7, 15, 16, 20, and 26), methods of treating an unspecified liver disease by gene therapy (claim 27), methods of treating an unspecified disease not limited to liver disease by gene therapy (claims 31-32), methods of gene therapy (claims 36 and 39), and pharmaceutical compositions for treating human disease (claim 43), in light of the specification, by the claimed methods. The methods involve administration of a recombinant adeno-associated virus, rAAV, to liver cells either *in vivo* or *ex vivo* followed by administration of the transduced liver cells. Although the method of claims (claims 1, 4, 7, 15, 16, 20, and 26) as claimed is not limited to gene therapy, the specification describes no other use for the claimed method. Therefore, in light of the specification claims (claims 1, 4, 7, 15, 16, 20, and 26) are interpreted as being directed to gene therapy, and are so evaluated for compliance of the specification with the enablement

requirement. The implied use of this method to evaluate AAV as a suitable gene therapeutic vector does not meet the utility requirement, and hence the enablement requirement for how-to-use, since such use would constitute using the invention for research on itself.

The specification provides general guidance limited largely to the listing of diseases that may be treated, therapeutic transgenes, promoters to be used to express the transgene with little guidance as to which promoters would be useful for which applications, a few methods of administration, and the teaching (see page 31, from line 15) regarding dosage and regimen of treatment that the skilled artisan should determine this by trial and error experimentation. The specification provides working examples only for transfer of rAAV that subsequently expresses human clotting factor IX to mouse liver *in vivo*. No working examples of gene therapy are provided, nor are suitable model systems described except for the use of hemophilic dogs for treatment with rAAV expressing factor IX. At page 10, lines 1-10 of the specification, it is stated that in such dogs retroviral vector-mediated gene therapy resulted in persistent, but subtherapeutic expression of factor IX, while adenoviral-mediated gene therapy resulted in brief therapeutic expression, but that immunotoxicity of the vector results interfering with extended expression. These problems are cited as the impetus to develop AAV vectors for transduction of liver cells for gene therapy.

Gene therapy is a highly unpredictable and undeveloped art. Orkin et al. reviews the infant state of the art of gene therapy from before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical

challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression that gene therapy is successful is mistaken (pages 1-2). The instant application provides no guidance beyond the prior art, and offers no solutions to these problems raised by Orkin et al. Orkin et al. provides little discussion on using AAV for gene therapy other than to say that little experience has been obtained due to the inability to produce large amounts of rAAV, which raises an issue of the suitability of AAV for gene therapy at the time the invention was made. The difficulty in preparing large amounts of rAAV for treatment is exacerbated by the low transduction efficiency. As taught by Russell et al. (Proc. Natl. Acad. Sci. USA 91: 8915-8919, 1994) it requires thousands of vector particles to are required to transduce a single dividing cell *in vitro,* lacking immune mediators, mucous secretions, digestive enzymes and other potential inhibitors of transduction likely to be encountered *in vivo*. Consequently, it is unclear how effective rAAV would be in gene therapy (see Russell et al., page 8919, para. 1). With respect to rAAV vectors for use in gene therapy, the lack of experience in their use is an additional source of unpredictability.

Fisher et al. (J. Virol. 70(1): 520-532, 1996) describes experiments on using rAAV vectors to transduce liver cells *in vitro* and *in vivo.* The reference concludes that the low efficiency of rAAV transduction limits its usefulness as a gene therapy vector unless further advances are made because of the step of converting a single-strand rAAV to double-strand, which requires helper virus functions. The reference also discloses the difficulty in producing suitable quantities of purified rAAV particles. (See Fisher et al., Abstract, page 520 for overview; para. bridging pages 520-521; page 527, col. 1, para. 1; para. bridging pages 529, 531 and 532). Chen et al. (Hum. Gen. Ther. 8: 125-135, 1997) discloses that the efficiency of AAV vectors for transduction and expression of clotting factor IX in cultured cells was lower than for retroviral vectors both in terms of transduction and expression (see Abstract, page 125, for overview). Koeberl et al. (Proc. Natl. Acad. Sci. USA 94: 1426-1431, 1997) carried out experiments similar to those disclosed in the working examples and achieved sustained levels of factor IX expression comparable to those reported in the instant specification. However, they noted that plasma levels of 1-2 ng/ml were far below therapeutic levels for humans of 100 ng/ml. As noted above, the specification teaches that retroviral delivery of a factor IX expression construct to hemophiliac dogs resulted in subtherapeutic expression. As shown by the art cited, rAAV delivery is not expected to be any better without some further advance requiring inventive experimentation and development.

In view of the unpredictable and undeveloped state of gene therapy as shown by the prior art, the minimal guidance in the specification on rAAV-mediated gene therapy in general and the

lack of guidance specific for the treatment of specific diseases, the lack of relevant working examples, the high unpredictability of gene therapy in the art, and the inventive experimentation that would be required to overcome the problems known in the art, it would require undue experimentation in order to practice the invention claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15, 31 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is indefinite as it is unclear at what point, if any, in the method the partial hepatectomy is to be carried out (rather than provided). Is the hepatectomy part of the method or simply a limitation on a prospective mammalian subject?

Claims 31 and 32 are indefinite for recitation of "specifically functions in liver cells" (claim 31). It is unclear how "specifically" in this context limits the scope of the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 16 and 26 are rejected under 35 U.S.C. 102(a) as being anticipated by Fisher et al. (J. Virol. 70(1): 520-532, 1996).

Fisher et al. disclose pharmaceutical compositions containing a recombinant AAV in a pharmaceutically acceptable carrier, the rAAV comprising in order an AAV ITR, a viral promoter, a polynucleotide encoding a polypeptide operatively linked to the promoter, a polyadenylation signal operatively linked to the polynucleotide, and a second AAV ITR, and a method of using same to express a polynucleotide in a mammal *in vivo*. The method comprises administering the rAAV to liver cells *in vivo* in the presence of a "secondary agent for enhancing transduction efficiency", i.e. a helper adenovirus. (See page 520, Abstract; para. bridging pages 521-522; page 525, Fig. 4B; page 526, col. 2.)

Claims 1 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Ponnazhagan et al. (Blood 86 (10, Suppl. 1): 240a, Abstract 948, Nov. 15, 1995).

Ponnazhagan et al. disclose a method of gene transfer by administering recombinant AAV viral particles to the liver vasculature of a mammal, e.g. mouse, wherein the AAV genome

encoded the human β-globin gene under control of its own promoter. It is noted that delivery of the viral particles through the tail vein was found to deliver the viral particles to the liver, and therefore the liver vasculature by inference.

Claims 1 and 26, are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Koeberl et al. (Am. J. Hum. Genet. 57(Suppl. 4): A43, 1995).

Koeberl et al. (1995) discloses a method of expressing a polynucleotide encoding a polypeptide in a mammal *in vivo* by direct injection of a rAAV vector, which comprised a Moloney MLV promoter operatively linked to a polynucleotide encoding the polypeptide, into mouse liver.

Claims 1, 4, 7, and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by Chiorini et al. (US 5,693,531).

Chiorini et al. discloses a method of expressing a polypeptide in a mammal by administering hepatocytes transduced with a rAAV comprising an expression cassette encoding a therapeutic protein relevant to inherited human liver disease, e.g. LDL receptor or ornithine transcarbamylase or an antisense molecule to treat hepatitis. The reference teaches that the cells can be injected into the portal vasculature. The vectors also comprise two AAV ITRs flanking the expression cassette. See col. 2, lines 7-10; col. 3, lines 4-57; col. 4, lines 44-67; col. 5, lines

1-25. Given the discussion of diseases in col. 4, human subjects for application for the method are implicit.

Claims 1, 4, 7, 15, 16, 20, 26, and 43 are rejected under 35 U.S.C. 102(e) as being anticipated by Wilson et al. (US 5,756,283).

Wilson et al. discloses methods for expressing polynucleotides in a mammal, such as human, by administering rAAV to liver cells *in vivo* together with either a helper virus or some other secondary AAV transduction efficiency enhancing product or transducing liver cells, e.g. hepatocytes, with a rAAV *ex vivo* in the presence of helper virus, e.g. adenovirus, and then administering the transduced cells to a mammal. The rAAV vectors comprise a transgene cassette comprising, in operative association, a promoter region, e.g. a CMV viral promoter, a polynucleotide encoding a product of interest and polyadenylation sequence with the cassette flanked by AAV ITR sequences. The polynucleotide can either encode a reporter protein or a therapeutic protein. The reference also discloses pharmaceutical compositions of a rAAV vector, either as a viral particle or as a transduced cell, in a pharmaceutically acceptable carrier. In embodiments, where the cells of the subject are removed from the liver for *ex vivo* transduction, a partial hepatectomy results. Administration to the liver can be through infusion into the portal vein. (see "Summary of Invention", col. 2-3 for overview; col. 6, lines 13-65; col. 7, line 43 to col. 9, line 46; col. 11, lines 8-54; col. 12, lines 17-22; col. 22, lines 1-49).

Conclusion

This is a continuation of applicant's earlier Application No. 08/882,044. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608.

Any inquiry concerning administrative, procedural or formal matters relating to this application should be directed to Patent Analyst Patsy Zimmerman whose telephone number is (703) 308-8338. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

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